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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/708,204	02/16/2004	Itzhak Bentwich	050992.0201.CPUS03	2203

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ROSETTA-GENOMICS
c/o PSWS
700 W. 47TH STREET
SUITE 1000
KANSAS CITY, MO 64112

EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/708,204	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/3/06 (2)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Response to Amendment

Applicant's amendments to the claims in the reply filed November 22, 2006, is acknowledged. Claims 31–42 are now pending in the application and examined herein.

Election/Restrictions

Applicant's election of Group I, drawn to an isolated nucleic acid, and to an RNA equivalent and vector thereof, without traverse, in the reply filed November 22, 2006, is acknowledged. Claims 31–42 are considered to read on Group I. Also acknowledged is applicant's election, with traverse, of SEQ ID NO:6527. Applicant's election of a single target gene, TNFRSF6, SEQ ID NO:5544 (Remarks, page 6), without traverse, is also acknowledged, but no longer relevant to the instant application, since the claims as presented on 11/22/06 neither recite nor claim TNFRSF6 or SEQ ID NO:5544.

Applicant's arguments traversing the restriction among the individual nucleotide sequences from claims 1-6, 17, 20-23, and 25 (now cancelled) have been fully considered but are not persuasive.

Applicants' reference to the U.S. Patent and Trademark Office policy regarding the examination of patent applications that claim large numbers of nucleotide sequences in the Official Gazette, 1192 O.G. 68 (November 19, 1996) is acknowledged, however, not found persuasive on the basis that this policy regarding the partial waiving of the requirements of 37 CFR 1.141 is such that it will permit a reasonable number of nucleotide sequences to be claimed

in a single application. Under the policy, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction. The waiver is permissive in nature and not a requirement. The waiver was written in 1996, well before the exponential growth of the nucleic acid databases.

Given that each sequence requires a separate search and consideration of the patent and non-patent literature, and given that a search of more than one (1) of the sequences claimed in the instant claims presents an undue burden on the Patent and Trademark Office due to the complex nature of the search in terms of computer time needed to perform the search and the subsequent analysis of the search results by the examiner, one (1) nucleotide sequence is considered to be a reasonable number of sequences for examination.

Additionally, rejoinder opportunities among individual sequences no longer exist in the instant application since no other sequences apart from SEQ ID NO:6527 are currently recited and there is no generic claim in the application which may be considered to link each of the sequences (MPEP §809).

The requirement is still deemed proper and is therefore made FINAL.

Sequences—Notice to Comply

A review of the instant claims shows that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).

However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements

For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

The drawings and specification do not comply with 37 CFR §1.821(d), which states:

> 37 CFR § 1.821 Nucleotide and/or amino acid sequence disclosures in patent applications –
>
> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In the instant case, the sequences shown in Figures 22B, 23B, and 24A are not identified with SEQ ID NO: identifiers as required by the Rules.

Applicant is requested to amend either the drawings or the Brief Description of the Drawings in the specification to assign each sequence a corresponding SEQ ID NO:

Applicants are also encouraged to review the entire disclosure for compliance with 37 CFR §1.821(d).

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Information Disclosure Statement

The information disclosure statement filed 10/3/06 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that

portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

In the instant case, Applicant indicates that copies of several references have not been provided in the instant case since the references have been provided in several other copending applications (see page 2 of 10/3/06 IDS), in compliance with 37 CFR §1.98(d).

However, this fails to comply with 37 CFR §1.98(d), which states

> A copy of any patent, publication, pending U.S. application or other information, as specified in paragraph (a) of this section, listed in an information disclosure statement is required to be provided, even if the patent, publication, pending U.S. application or other information was previously submitted to, or cited by, the Office in an earlier application, unless:
>
> (1) The earlier application is properly identified in the information disclosure statement and is relied on for an earlier effective filing date under 35 U.S.C. **120**; and
>
> (2) The information disclosure statement submitted in the earlier application complies with paragraphs (a) through (c) of this section.

In the instant case, many of the other copending applications referred to by Applicant are not relied upon for an earlier effective filing date under 35 U.S.C. **120**. For instance 10/310,914, 10/321,503, and so on.

Accordingly, copies of references must be supplied in the instant application even if the patent, publication, pending U.S. application or other information was previously submitted to the Office in another application.

Claim Objections

Claims 34, 36, 37, 38, 40, and 42 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 37 and 38 are drawn to the nucleic acid of claim 32 and 35, respectively, "wherein the nucleic acid is an RNA." However, a review of the sequence listing shows that SEQ ID NO:6527 and SEQ ID NO:15 are 131-nucleotide and 22-nucleotide RNAs, respectively, and broadest reasonable interpretation of independent claims 31 and 34 do not appear to include DNA, unless it is applicant's contention that a 140-mer may comprised SEQ ID NO:6527 plus 9 deoxyribonucleotides. However, the specification does not support this interpretation.

Claim 34 recites the nucleic acid of claim 31, wherein the nucleic acid "consists of" (a), (b), (c), or (d). The transitional phrase "consists of" instead of "comprises", as used in claim 31, does not further limit the scope of the invention, since the preamble of claim 31 requires that the nucleic acid consist of 19 to 140 nucleotides. The transitional phrase prefacing Parts a–d does not alter the scope thereof. Claims 36, 40, and 42 are objected to therefor due to their dependence on claim 34.

Accordingly, "wherein the nucleic acid is RNA" does not appear to further limit the invention or narrow the scope of the invention now claimed in claims 32 and 35.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31–42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 31, the base claim, reads as follows:

> 31. (new) An isolated nucleic acid consisting of 19 to 140 nucleotides wherein the sequence of the nucleic acid comprises: (a) at least 19 consecutive nucleotides of SEQ ID NO: 6527; (b) an RNA equivalent of (a); (c) a sequence at least 80% identical to (a) or (b); or (d) the complement of any one of (a)-(c).

Thus, although directed to a single polynucleotide sequence, the metes and bounds of the claims are unclear. This is primarily due to the limitations recited in Parts b-d, wherein the isolated nucleic acid may be an RNA equivalent of (a); (c) a sequence at least 80% identical to (a) or (b); or (d) the complement of any one of (a)-(c).

The scope and precise meaning of the term "RNA equivalent" is unclear, rendering the true breadth of the claim as a whole unclear. The structures clearly included or excluded by the claim are nebulous at best. Compounding this ambiguity are the recitations in Parts c and d, which claim sequences 80% identical to any RNA equivalent and/or complements of sequences that are 80% identical to any RNA equivalent. If it cannot be ascertained what is meant by "an RNA equivalent," it cannot be ascertained what is meant by structures 80% identical to an RNA equivalent.

Broadest reasonable interpretations of these alternative structures and embodiments of the claimed nucleic acid would appear to include nearly any polyribonucleotide sequence no matter how distant or closely related, with almost any degree of homology to SEQ ID NO:6527. However the specification fails to ascribe credible, specific, or substantial utilities to all these inventions and such an interpretation would seem at best to be speculation, conjecture, and assumption. As a result, the claims and the specification fail to adequately inform one of skill in the art as to which structures are excluded or included by the claims.

While the metes and bounds of the limitations "at least 80% identical to" and "complement of" are clear and understood, they are rendered vague and ambiguous when filtered through the limitation "RNA equivalent of."

Independent claim 31 and dependent claim 34 both recite the limitations "an RNA equivalent," "a sequence at least 80% identical to [an RNA equivalent]," and "the complement of [an RNA equivalent]" of SEQ ID NO:6527.

The scope and meaning of the term "RNA equivalent" is unclear. The term is defined neither in the claim nor the specification in a manner that would clearly apprise one of skill in the art of the metes and bounds of the limitation. As a result, the metes and bounds of the claim as a whole are unclear.

The sequence listing as originally filed defines SEQ ID Nos. 6527 and 15 as 131- and 22-nucleotide RNAs, respectively. Thus, it is unclear, for example, what structures do or do not fall within the scope of an RNA equivalent of an RNA.

Dependent claims 32, 33, and 35-42 are rejected for the same reasons due to their dependence on claim 31 and/or 34.

Clarification or correction is required.

***

Claims 32, 35, 37, and 38 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the recitation "wherein the at least 19 nucleotides comprises the sequence of SEQ ID NO:15" in claims 32 and 35 (claims 37 and 38 depend form 32 and 35, respectively).

SEQ ID NO:15 is a 22-mer. It is unclear how a 19-, 20-, or 21-mer may comprise a 22-mer.

Clarification or correction is required.

Claim Rejections - 35 USC § 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31–42 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific and/or substantial asserted utility, a credible asserted utility, or a well established utility.

The claims are drawn to an isolated nucleic acid sequence consisting of 19 to 140 nucleotides, wherein the sequence comprises a) at least 19 consecutive nucleotides of SEQ ID NO: 6527; b) an RNA equivalent of (a); c) a sequence at least 80% identical to (a) or (b); or d) the complement of any one of (a)-(c).

Also claimed are nucleic acids comprising SEQ ID NO:15, a 22-nucleotide sequence located withing SEQ ID NO:6527, and vectors and probes of any of the above.

Thus, although directed to a single polynucleotide sequence, the claims are extremely broad. This is primarily due to the limitations recited in Parts b-d, wherein the isolated nucleic acid may be an RNA equivalent of (a); (c) a sequence at least 80% identical to (a) or (b); or (d) the complement of any one of (a)-(c).

Importantly, and as explained above, the scope and precise meaning of the term "RNA equivalent" is unclear, rendering the true breadth of the claim itself unclear. The structures clearly included or excluded by the claim are nebulous at best. Compounding this ambiguity are the recitations in Parts c and d, which claim sequences 80% identical to any RNA equivalent and/or complements of sequences that are 80% identical to any RNA equivalent.

Reasonable interpretations of these alternative structures and embodiments of the claimed nucleic acid would appear to include nearly any polyribonucleotide sequence no matter how distant or closely related, with almost any degree of homology to SEQ ID NO:6527.

The specification teaches that the disclosed, bioinformatically detected nucleic acids such as SEQ ID NO:6527 relate to genomic address messenger or GAM oligonucleotides that selectively inhibit translation of known target genes, which may be involved in various diseases, it would appear that the utility of the methods and reagents claimed and disclosed would depend

on their ability to specifically hybridize to and, thereby, possibly inhibit or modulate the function of SEQ ID NO:6527 or its predicted target gene.

The specification teaches that the GAMs are bioinformatically predicted to be micro RNAs (miRNAs), short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

Citing from the published application (U.S. 20050222399 A1), the specification states, for example, that "The oligonucleotides of the present invention represent [...] a dimension comprising a huge number of non-protein coding oligonucleotides which modulate expression of thousands of proteins and are associated with numerous major diseases" (paragraph 41).

In paragraphs 64–67, the specification appears to assert or suggest that some (it is not stated which) of the disclosed, bioinformatically detectable sequences may share homology with genes associated with or causally related to Alzheimer's disease. Along these lines, a long list of potential gene targets is provided.

Table 8 of the application, presumably on the basis of complementarity to sequences in SEQ ID NO:6527, teaches that a function of GAM1032 (SEQ ID NO:6527) is to inhibit Choline Acetyltransferase, CTSK, Myeloperoxidase, Serine (or cysteine) Proteinase Inhibitor, Beta- site APP- cleaving Enzyme, and TNFRSF6, the gene products of all which are said by Table 8 to contribute or correlate with the symptoms and/or progression of Alzheimer's. Table 8 cites several references for each gene target, which are said to provide evidence for the relationship between the putative target gene and its possible function in Alzheimer's.

The specification also teaches how to detect and validate the expression of GAMs in cells.

However, a review of the specification, drawings, claims, sequence listings, and computer listings as filed fails to find any specific disclosure clearly establishing a nexus between the claimed nucleic acid sequences SEQ ID NO:6527 and 15 and the treatment, diagnosis, or identification of any disease or disorder. Similarly, no disclosure is found clearly establishing a direct link between the claimed nucleic acid sequences and the inhibition or augmentation of any gene or gene product. Although the prior art may recognize that certain genes play significant roles in the development or progression of Alzheimer's disease, neither the prior art nor the instant application provide any evidence establishing a link between the expression of the claimed nucleic acid sequences and the treatment of Alzheimer's disease, nor any evidence that the claimed nucleic acid, SEQ ID NO:6527, when it expressed in the cell will be processed into an miRNA fragment such as SEQ ID 15 that itself will provide for a treatment effect or even down-regulation of a specific target.

Accordingly, no evidence is found in the instant application or the prior art for the assertions that the instantly claimed sequences may be used for any specific, substantial, or credible utility, much less for the treatment of Alzheimer's disease.

Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences disclosed in the instant application appears to be based purely on bioinformatic methods for predicting RNA folding and miRNA-like hairpins, followed by alignment analysis to predict potential gene targets. Once likely gene targets are identified, the published literature is

searched to identify possible correlations between the gene and disease states or genetic disorders.

The instant application provides no evidence that the "novel" bioinformatically detectable nucleic acids are expressed in any cell or tissue in culture or *in vivo*, nor any evidence showing or suggesting that, if expressed in culture or *in vivo* the claimed nucleic acids will regulate any particular gene, nor any evidence that the regulation of that gene will provide for any treatment effect of any disease.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. That is no evidence is present verifying the expression of instant SEQ ID NO:6527 in any cell line much less a human cell line or that its expression or absence thereof has been correlated any disease, neurological or otherwise, or trait.

Further, Applicant has not provided evidence that instant SEQ ID NO: 6527 is up or down regulated in any cell or tissue, animal or bacteria, or plays any role in the predisposition of human or mammalian cells to any disease or condition.

Applicant's asserted utility appears to be based only on the predicted structure and sequence complementarity of SEQ ID NO: 6527 and, possibly, on various reports in the prior and/or post-filing art describing functions of the target gene or genes. From this, Applicant appears to extrapolate and thereby assert that inhibiting or somehow altering the expression of the purported target is beneficial, i.e., has utility, and that because SEQ ID NO: 6527 has a predicted miRNA-like precursor structure and a sequence that is complementarity to a known gene it plays a role in the susceptibility or predisposition of a subject to a disease or disorder.

However, this assertion is not credible. While sequences within SEQ ID NO: 6527 may have complementarity to a gene encoding a known protein, applicant has not presented any evidence or established any nexus that SEQ ID NO: 6527 is even expressed, or if expressed artificially will target and/or inhibit a particular gene, much less that the expression or inhibition or measurement of expression of SEQ ID NO: 6527 may be used to prevent, treat, or diagnose a disease or condition. The asserted utility is speculative.

The absence, over- or under-expression, or mutated expression of almost any gene may directly or indirectly cause disease. Given the billions of nucleotides in the human genome, one of skill may bioinformatically examine and detect, with varying degreess of success, a number of miRNA-like structures, and, based on its homology to a known gene, propose that it regulates a complementary gene. This, however, this is insufficient to clearly establish a link between a claimed bioinformatically detected sequence and a utility as a therapeutic or diagnostic agent, when the post-filing art indicates that a number of analyses are necessary to confirm expression and function.

Thus, while the asserted utility may be specific and substantial, it is not credible. The specification does not establish a nexus between any particular disease state, and an altered level or form of the claimed SEQ ID NO:6527 that would enable one of skill to use SEQ ID NO:6527 to achieve a beneficial effect.

In addition to the bioinformatically predicted utility, described above, the specification generally asserts that Genomic Address Messenger sequences such as instant SEQ ID NO:6527 may be used in various ways. However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial.

For example, the specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel

oligonucleotides of the present invention and disease, for disease diagnosis and prevention purposes, and for monitoring disease progress, and for identifying gene targets.

This asserted utility is neither specific nor substantial. Since the same can be done with any polynucleotide, the asserted utility is not specific. Also, because the specification does not disclose any specific function for SEQ ID NO:6527, aside from indicating that it may be expressed in certain cells or present in certain genomes, it is unclear how or why one of skill in the art would use the information obtained by measuring SEQ ID NO:6527 expression for any particular purpose aside from general research. Further, since Applicant does not identify whether abnormal SEQ ID NO:6527 expression is causally related to any disease or condition, or whether abnormal SEQ ID NO:6527 function (e.g., a polymorphism) predisposes anyone to any disease or condition, the only recognizable utility of diagnostic probes is as tools for scientific research, and with no indication that anything useful will be discovered. Therefore, the asserted utility is not substantial since the application provides no teaching regarding how to use the probes or expression data for any practical purpose beyond the art-recognized methods of gene expression analysis.

Accordingly, polynucleotide probes derived from the instant invention are simply research intermediates that may help scientists isolate the gene and conduct further experimentation. Such probes can only be used to detect or amplify the genetic material having the same structure as the probes themselves. The probes would provide no immediate, real-world information about the overall structure or function of the underlying gene, for example, aside from its expression patterns.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO:6527, much less the recited RNA equivalents thereof have any specific biological function. No evidence or information is found either in the specification or the prior art linking SEQ ID NO:6527 with the modulation of any eukaryotic or mammalian gene or with the conditions that render cells or hosts susceptible to any biological condition, for example. No convincing evidence is found teaching any biological function for SEQ ID NO:6527 at all. In fact, no evidence is found suggesting or stating that SEQ ID NO:6527 has been made, isolated, cloned, detected, expressed, or even analyzed in a living cell *in vitro* or *in vivo.*

In summary, no biological or biochemical function has been assigned to SEQ ID NO:6527, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to an miRNA precursor and have some direct or indirect relation to a disease, such as Alzheimer's.

Thus, Applicant has not demonstrated that SEQ ID NO:6527 may be used in any mode of therapy or as a general means to define and treat bacterial infections.

Thus, the proposed utility of SEQ ID NO:6527 and 15 as a therapeutic target or agent, or material resource for preparing diagnostic probes, vectors, a host cells, are simply starting points for further research and investigation into potential practical uses of the claimed polynucleotide.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

> ...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific, substantial, or credible utility for SEQ ID NO:6527 or 15, much less any of the RNA equivalents or complements of SEQ ID NO:6527. No target gene has been conclusively identified nor has any evidence been presented showing a functional link between SEQ ID NO:6527 and any target gene, disease or genetic condiion, biological function or disorder. A credible, specific, and substantial nexus has not been established.

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Claims 31-42 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 31, 33, 34, 36, and 39–42 are rejected under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (U.S. Patent Application Publication 2005/0059005 A1).

Tuschl et al. disclose pre-processed and processed, or mature, miRNA sequences from vertebrate and invertebrate species. Specifically, Tuschl et al. teach two separate 22-nucleotide RNAs that are at least 80% identical to: (a) a nucleic acid comprising at least 19 consecutive nucleotides of SEQ ID NO:6527, and/or (b) an RNA equivalent of (a), as recited in instant claims 31 and 34 (see alignments and search results below. For all sequence search results see The Supplemental Complex Repository for Examiners (SCORE).

Tuschl et al. further teach procedures for recombinantly expressing pre-processed and mature miRNAs from vectors (paragraphs 19 and claim 12, for example), and for detecting miRNAs via Northern blotting using nucleic acid probes (paragraphs 34, 35, 39, and 43).

Accordingly, Tuschl et al. anticipate the instant claims.

RESULT 8
US-10-490-955-179
; Sequence 179, Application US/10490955
; Publication No. US20050059005A1
; GENERAL INFORMATION:
; APPLICANT: Tuschl, Thomas
; APPLICANT: Lagos-Quintana, Mariana
; APPLICANT: Lendeckel, Winfried
; APPLICANT: Meyer, Jutta
; APPLICANT: Rauhut, Reinhard
; TITLE OF INVENTION: MicroRNA Molecules
; FILE REFERENCE: 2923-613
; CURRENT APPLICATION NUMBER: US/10/490,955
; CURRENT FILING DATE: 2004-03-29
; PRIOR APPLICATION NUMBER: PCT/EP02/10881
; PRIOR FILING DATE: 2002-09-27
; PRIOR APPLICATION NUMBER: EP 02 016 772.2
; PRIOR FILING DATE: 2002-07-26
; PRIOR APPLICATION NUMBER: EP 02 006 712.0
; PRIOR FILING DATE: 2002-03-22
; PRIOR APPLICATION NUMBER: EP 01 123 453.1
; PRIOR FILING DATE: 2001-09-28
; NUMBER OF SEQ ID NOS: 562
; SOFTWARE: PatentIn version 3.2
; SEQ ID NO 179
; LENGTH: 22
; TYPE: RNA

; ORGANISM: Mus musculus
US-10-490-955-179

Query Match 88.2%; Score 19.4; DB 10; Length 22;
Best Local Similarity 95.2%; Pred. No. 20;
Matches 20; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

Qy 1 CUAGACUGAAGCUCCUUGAGG 21
||||||| ||||||||||
Db 1 CUAGACUGAGGCUCCUUGAGG 21

RESULT 9
US-10-490-955-519
; Sequence 519, Application US/10490955
; Publication No. US20050059005A1
; GENERAL INFORMATION:
; APPLICANT: Tuschl, Thomas
; APPLICANT: Lagos-Quintana, Mariana
; APPLICANT: Lendeckel, Winfried
; APPLICANT: Meyer, Jutta
; APPLICANT: Rauhut, Reinhard
; TITLE OF INVENTION: MicroRNA Molecules
; FILE REFERENCE: 2923-613
; CURRENT APPLICATION NUMBER: US/10/490,955
; CURRENT FILING DATE: 2004-03-29
; PRIOR APPLICATION NUMBER: PCT/EP02/10881
; PRIOR FILING DATE: 2002-09-27
; PRIOR APPLICATION NUMBER: EP 02 016 772.2
; PRIOR FILING DATE: 2002-07-26
; PRIOR APPLICATION NUMBER: EP 02 006 712.0
; PRIOR FILING DATE: 2002-03-22
; PRIOR APPLICATION NUMBER: EP 01 123 453.1
; PRIOR FILING DATE: 2001-09-28
; NUMBER OF SEQ ID NOS: 562
; SOFTWARE: PatentIn version 3.2
; SEQ ID NO 519
; LENGTH: 22
; TYPE: RNA
; ORGANISM: Unknown
; FEATURE:
; OTHER INFORMATION: D. melanogaster or H. sapiens or M. musculus or C. elegans or
; OTHER INFORMATION: HeLa cells
US-10-490-955-519

Query Match 88.2%; Score 19.4; DB 10; Length 22;
Best Local Similarity 95.2%; Pred. No. 20;
Matches 20; Conservative 0; Mismatches 1; Indels 0; Gaps 0;

Qy 1 CUAGACUGAAGCUCCUUGAGG 21
||||||| ||||||||||
Db 1 CUAGACUGAGGCUCCUUGAGG 21

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner Art Unit 1635
January 9, 2007

SEAN M'GARRY
PRIMARY EXAMINER
AU 1635

Notice to Comply	Application No. 10/708204	Applicant(s) BENTWICH, ITZHAK	
	Examiner Louis V. Wollenberger	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing Error Report."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: *Sequences in Figs. 22B, 23B, and 24A are not identified with SEQ ID NO: identifiers.*

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:
For Rules Interpretation and PatentIn Software, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2533.
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